HMGCL gene

3-hydroxymethyl-3-methylglutaryl-CoA lyase

Normal Function

The *HMGCL* gene provides instructions for making an enzyme called 3-hydroxymethyl-3-methylglutaryl-CoA lyase (HMG-CoA lyase). This enzyme is found in mitochondria, which are the energy-producing centers inside cells. HMG-CoA lyase plays a critical role in breaking down proteins and fats from the diet. Specifically, it is responsible for processing leucine, a protein building block (amino acid) that is part of many proteins. HMG-CoA lyase also produces ketones during the breakdown of fats. Ketones are compounds that certain organs and tissues, particularly the brain, use for energy when the simple sugar glucose is not available. For example, ketones are important sources of energy during periods of fasting.

Health Conditions Related to Genetic Changes

3-hydroxy-3-methylglutaryl-CoA lyase deficiency

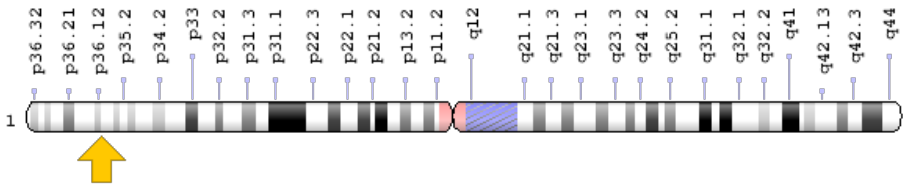
More than 25 mutations in the *HMGCL* gene have been identified in people with 3-hydroxymethyl-3-methylglutaryl-CoA lyase deficiency (also called HMG-CoA lyase deficiency). Most of these mutations change single amino acids in the HMG-CoA lyase enzyme. For example, the most common mutation in the Saudi Arabian population replaces the amino acid arginine with the amino acid glutamine at position 41 (written as Arg41Gln or R41Q). Other *HMGCL* mutations result in the production of an abnormally short enzyme that is missing critical segments.

If a mutation reduces or eliminates the activity of HMG-CoA lyase, the body is unable to process leucine or make ketones properly. When leucine is not processed normally, chemical byproducts called organic acids can build up and make the blood too acidic (metabolic acidosis). A shortage of ketones can cause blood sugar levels to become dangerously low (hypoglycemia). The effects of metabolic acidosis and hypoglycemia can damage cells, particularly in the brain, resulting in serious illness in children with HMG-CoA lyase deficiency.

Chromosomal Location

Cytogenetic Location: 1p36.11, which is the short (p) arm of chromosome 1 at position 36.11

Molecular Location: base pairs 23,801,877 to 23,825,459 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- 3-hydroxy-3-methylglutarate-CoA lyase
- 3-hydroxy-3-methylglutaryl-Coenzyme A lyase
- 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase
- HL
- HMG-CoA lyase
- HMGCL_HUMAN

Additional Information & Resources

Educational Resources

- Basic Neurochemistry (sixth edition, 1998): Disorders of Organic Acid Metabolism https://www.ncbi.nlm.nih.gov/books/NBK27945/#A3112

Scientific Articles on PubMed

- PubMed https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28HMGCL%5BTIAB%5D%29+OR+%28HMG+CoA+lyase%5BTIAB%5D%29+OR+%283-hydroxy-3-methylglutaryl-Coenzyme+A+lyase%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

OMIM

- 3-HYDROXY-3-METHYLGLUTARYL-CoA LYASE http://omim.org/entry/613898

Research Resources

- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=HMGCL%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=5005
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/3155
- UniProt
  http://www.uniprot.org/uniprot/P35914

Sources for This Summary

- Al-Sayed M, Imtiaz F, Alsmadi OA, Rashed MS, Meyer BF. Mutations underlying 3-hydroxy-3-methylglutaryl CoA lyase deficiency in the Saudi population. BMC Med Genet. 2006 Dec 16;7:86.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17173698
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1764877/
- Ashmarina LI, Pshezhetsky AV, Branda SS, Isaya G, Mitchell GA. 3-Hydroxy-3-methylglutaryl coenzyme A lyase: targeting and processing in peroxisomes and mitochondria. J Lipid Res. 1999 Jan;40(1):70-5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9869651
- Cardoso ML, Rodrigues MR, Leão E, Martins E, Diogo L, Rodrigues E, Garcia P, Rolland MO, Vilarinho L. The E37X is a common HMGCL mutation in Portuguese patients with 3-hydroxy-3-methylglutaric CoA lyase deficiency. Mol Genet Metab. 2004 Aug;82(4):334-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15308132
- Casals N, Gómez-Puertas P, Pié J, Mir C, Roca R, Puisac B, Aledo R, Clotet J, Menao S, Serra D, Asins G, Till J, Elias-Jones AC, Cresto JC, Chamoles NA, Abdenur JE, Mayatepek E, Besley G, Valencia A, Hegardt FG. Structural (betaalpha)8 TIM barrel model of 3-hydroxy-3-methylglutaryl-coenzyme A lyase. J Biol Chem. 2003 Aug 1;278(31):29016-23. Epub 2003 May 13.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12746442
- Fu Z, Runquist JA, Forouhar F, Hussain M, Hunt JF, Miziorko HM, Kim JJ. Crystal structure of human 3-hydroxy-3-methylglutaryl-CoA Lyase: insights into catalysis and the molecular basis for hydroxymethylglutaric aciduria. J Biol Chem. 2006 Mar 17;281(11):7526-32. Epub 2005 Dec 5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16330550
- Pie J, Casals N, Puisac B, Hegardt FG. Molecular basis of 3-hydroxy-3-methylglutaric aciduria. J Physiol Biochem. 2003 Dec;59(4):311-21.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15164951

- Pié J, López-Viñas E, Puisac B, Menao S, Pié A, Casale C, Ramos FJ, Hegardt FG, Gómez-Puertas P, Casals N. Molecular genetics of HMG-CoA lyase deficiency. Mol Genet Metab. 2007 Nov;92(3):198-209. Epub 2007 Aug 9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17692550
- Puisac B, López-Viñas E, Moreno S, Mir C, Pérez-Cerdá C, Menao S, Lluch D, Pié A, Gómez-Puertas P, Casals N, Ugarte M, Hegardt F, Pié J. Skipping of exon 2 and exons 2 plus 3 of HMG-CoA lyase (HL) gene produces the loss of beta sheets 1 and 2 in the recently proposed (beta-alpha)8 TIM barrel model of HL. Biophys Chem. 2005 Apr 1;115(2-3):241-5. Epub 2005 Jan 6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15752612

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